PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC32099A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2005/000382	International filing date *(day/month/year)* 14.02.2005	Priority date *(day/month/year)* 27.02.2004
International Patent Classification (IPC) or national classification and IPC INV. G01N33/68		
Applicant PFIZER JAPAN, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 14 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.03.2005	04.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Boiangiu, C Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2005/000382

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-38 as originally filed

Sequence listings part of the description, Pages

1-23 as originally filed

Claims, Numbers

1-26 as originally filed

Drawings, Sheets

1/9-9/9 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14,21-26

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 14,21-26

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-13,15-20 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9,10,12,13,17-20
	No:	Claims	1, 2-4, 6, 7,11,15 ,16
Inventive step (IS)	Yes:	Claims	9
	No:	Claims	1, 2-4, 5-8,10-13, 15-20
Industrial applicability (IA)	Yes:	Claims	1-13,15-20
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item V.

1. Reference is made to the following documents:

D1 : WO 99/64452 A (SMITHKLINE BEECHAM CORPORATION) 16 December 1999 (1999-12-16)

D2 : WO 00/08155 A (INCYTE PHARMACEUTICALS, INC; HILLMAN, JENNIFER, L; YUE, HENRY; LAL, PR) 17 February 2000 (2000-02-17)

D3 : WO 02/059344 A (MERCK &; CO., INC; LIU, QINGYUN; CLEMENTS, MICHELLE; MCDONALD, TERRENCE) 1 August 2002 (2002-08-01)

D4 : DATABASE Geneseq [Online] 11 April 2000 (2000-04-11), XP002330409; retrieved from EBI accession no. GSP:AAY58645 Database accession no. AAY58645

D5 : DATABASE Geneseq [Online] 31 May 2000 (2000-05-31), XP002330411; retrieved from EBI accession no. GSP:AAY69989 Database accession no. AAY69989

D6: DATABASE Geneseq [Online] 4 March 2003 (2003-03-04). XP002330412 retrieved from EBI accession no. GSP:ABP82002 Database accession no. ABP82002

D7: DATABASE UniProt [Online] 16 October 2001 (2001-10-16). XP002330587 retrieved from EBI accession no. UNIPROT:GPR35_MOUSE Database accession no. GPR35_MOUSE

D8: DATABASE UniProt [Online] 1 March 2003 (2003-03-01). XP002330588 retrieved from EBI accession no. UNIPROT:Q8CB97 Database accession no. Q8CB97

D9: DATABASE EMBL [Online] 21 November 2002 (2002-11-21). XP002330589 retrieved from EBI accession no. EM_HTG:AC137209 Database accession no. AC137209

2. Non Unity

This Authority considers that there are 6 inventions covered by the claims indicated as follows:

I: Claims 1-13,15-20 directed to method of screening for a compound that modulates GPR35 protein.

II: Claims 14,21-26 (partially) directed to zaprinast and derivatives thereof as:
5-(2-ethoxyphenyl)-1,4-dihydro-7H-1,2,3-Triazolo[4,5-d]pyrimidin-7-one,
3-(4,7-dthydro-7-oxo-1H-1,2,3-triazolo[4,5-d]pyrimidin-5-yl)-4-propoxy-benzenesuifonyl chloride,
3-(4,7-dihydro-7-oxo-1H-1,2,3-triazolo[4,5-d]pyrimidin-5-yl)-4-propoxy-berizenesulfonamide
,
6-phenyl-1-(phenylmethyl)-1H-bis[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)-4(5H)-one
and use thereof to modulate GPR35 protein.

III: Claim 23 (partially) directed to a medicament comprising a compound selected from the group consisting of the following compounds;
2-methyl-5-phenyl-pyrazolo[1,5-a]pyrimidin-7(4H)-one,
3(-4,7dihydro-1-methyl7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxy-benzenep ropanoic acid,
3-[3'(4,5-dihydro-methyl-4-oxo-1-propyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-propoxypheny 1]-2-propenoic acid,
2,4-dihydro-2-methyl-5-[2-(2-methylpropoxy)-5-(1H-tetrazol-5-yl)-3-pyridinyl]-3-propyl-7H-p yrazolo[4,3-djpyrimidin-7-one,
2,4-dihydro-2-methyl-5-[2-(2-methylpropoxy)-5-(1H-1,2,3-triazol-4yl)-3-pyridinyl]-3-propyl-7 H-pyrazolo[4,3-djpyrimidin-7-on

IV: Claim 23 (partially) directed to a medicament comprising;
5-Nitro-2-(3-phenylpropylamino)benzoic acid

V: Claim 23 (partially) directed to a medicament comprising;
2-Cyano-4-hydroxyindole

VI: Claim 23 (partially) directed to a medicament comprising;
2-(2-Propoxyphenyl)-8-trifluoromethylpurin-6-one

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The technical feature of method **claim 1** resides in the step of observing the effect of the candidate compounds on GPR35 protein activity in a screening assay. Neither the same nor a corresponding special technical feature is present in any of compounds disclosed in

claims 14 and **23.** No manufacturing relationship exists between the screening method and the claimed compounds. Further, the screening method is not a method of using compounds of **claims 14** and **23**. In the absence of any teaching as to the structure required for a compound to act as a GPR35 protein modulator, there is no single general concept that links the method to the claimed compounds.

The compounds of **claims 14** and **23** would be regarded as having the same or corresponding technical feature if they had a common property or activity, and shared a significant structural element that is essential to the common property or activity. While the compounds of **claims 14** and **23** do share the common property of modulating GPR35 activity, there is no teaching as to a shared significant structural element between the groups of compounds of the different inventions (see above compounds structure of inventions II-VI), and hence, there is no disclosure of the same or corresponding technical feature. However, within each group of inventions a structural element was found that links the compounds together.
Thus, unity of invention is lacking (a priori) between the screening method and each of the groups of compounds indicated.

In addition, it is to be noted that in **D1** the compounds that modulate GPR35 protein are potential modulators of the digestive system and the neural activity (**D1**: page 3, lines 10-24). Therefore, the very technical problem that the present application tries to solve, namely to identify the function of GPR35, has already been anticipated by the teaching of **D1.** In view of **D1** there can be no single general inventive concept. Thus, unity of invention is lacking (a posteriori).

The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT. The applicant has been invited to pay five additional search fees but has chosen to reject this proposition. Hence, an opinion as to novelty, inventive step and industrial applicability shall be restricted to the group of invention 1.

3. Novelty

3.1 Independent claims

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of **claims 1, 2-4, 6, 7, 11** is not new in the sense of Article 33(2) PCT.

3.1.1. Claims 1, 2-4, 6, 7 and 11

Document **D1** discloses (**D1**: abstract; description: page 1, lines 3-6; page 3, lines 10-24; page 13, line 21- page 14, line 1; page 14, lines 6-20; page 15, lines 10-13; page 16, lines 1-18; page 26, example 8; claims 4-11):

a. A method of screening for a compound that modulates a GPR35 protein, comprising the step of contacting a GPR35 protein or a partial polypeptide thereof with a test compound (**D1**: abstract; description: page 1, claim 6).
Therefore, the subject-matter of **claim 1** is not new.

b. D1 further discloses: A method of screening for a compound used in the treating of diseases associated with GPR35 imbalance (e.g. neurological or digestive disorders), comprising the steps of contacting a GPR35 protein or a partial polypeptide thereof with a test compound (**D1**: abstract; description: page 1, lines 3-6; page 3, lines 10-24; page 13, line 21- page 14, line 1; page 16, lines 1-18; claim 6).

Therefore, the subject-matter of **claims 2 and 3** is not new.

c. D1 also discloses: A method of screening for a compound that inhibits the binding of a ligand to a GPR35 protein, comprising the steps of (a) contacting a GPR35 protein or a partial polypeptide thereof with the ligand (b) contacting a GPR35 protein or a partial polypeptide thereof prepared in the substantially same manner as the one used in the step (a) with the ligand prepared in the substantially same manner as the one used in the step (a), in the presence of a test compound, and (e) comparing the results of the step (a) and the step (b) to determine whether the binding of the ligand is affected by the presence of the test compound (**D1**: description: page 3, lines 10-24; page 13, line 21- page 14, line 1; page 14, lines 12-20; page 15, lines 10-13; page 16, lines 10-18; page 25, example 3; claim 6).

d. D1 also discloses: A method of screening for a compound that is an agonist of a

GPR35 protein, comprising the steps of (a) adding a test compound to cells expressing a GPR35 protein or a partial polypeptide thereof or to a membrane fraction from the cells and (b) determining whether a functional response is observed (**D1**: abstract; description: page 1, lines 3-6; page 3, lines 10-24; page 13, line 21- page 14, line 1; page 15, lines 10-13; page 26, example 6; claims 6); and

e. A method of screening for a compound that is an antagonist of GPR35 protein, comprising the steps of (a) adding an agonist to cells expressing GPR35 protein or a partial polypeptide thereof or to a membrane fraction from the cells (b) adding an agonist prepared in the substantially same manner as the one used in the step (a) and a test compound to the cells or the membrane prepared in the substantially same manner as the one used in the step (a), and (c) comparing a functional response in the step (a) and one in the step (b) to determine whether the functional response is reduced by the test compound (D1: page 3, lines 10-24; page 14, lines 12-20; page 15, lines 10-13; claims 6).

Therefore, the subject-matter of **claims 4, 6 and 7** is not new.

f. D1 also discloses: A method of screening for a compound for use in the treatment or prevention of diseases associated with inappropriate GPR35 activity or level; e.g. pain, anxiety convulsions, eating disorders, Parkinson's disease, Huntington's disease, Alzheimer's disease, diarrhea, emesis, gastro-esophageal reflux disease,... (**D1**: description: page 1, lines 3-6; page 3, lines 10-24; page 16, lines 1-18; page 26, claims 4 and 6).

Therefore, the subject-matter of **claim 11** is not new.

3.2. Dependent claims

3.2.1. Claims 15 and 16

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of **claims 15** and **16** is not new in the sense of Article 33(2) PCT.

a. Examples of GPR35 proteins or fragments thereof and of encoding polynucleotide

sequences , which include at maximum **85.3%** identity with coresponding Seq-ID 2 and **99.7%** identity with Seq-ID 1, wherein the sequences have the same activity as Seq-ID 2 are given in **D4-D9** (see above accession numbers).
Therefore, only the sequences of **claims 15 (a),(c)-(e)** and **16 (a)** are new.
Therefore, the subject-matter of claims **15 (b)** and **16 (b)-(e)** is not new.

3.2.2. Claim 13

Methods of screening for compounds that modulate GPR35 activity by contacting a sequence of 99.7% identity to Seq-ID 4 with a test compound, is disclosed in **D1** (**D1**: description: page 1, lines 3-6; page 3, lines 10-24; page 13, line 21- page 14, line 1; page 14, lines 12-20; page 15, lines 10-13; claims 1 and 6; sequences Seq-ID1 and 2).
Therefore, the subject-matter of **claim 13 (b)-(e)** concerning the **Seq-ID 4** is not new.

Moreover, human or mouse GPR35 proteins are known in the prior art (e.g. D4 and D7 and see also in the present application: page 4, lines 28-30).
Therefore, the subject-matter of **claim 13 (f)** concerning the **human or mouse GPR35 proteins** is not new.

3.2.3. Claim 9

None of the prior art documents discloses or suggests zaprinast and analogue thereof as modulator of the GPR35 protein activity.
Therefore, the subject-matter of **claim 9** is new.

4. Inventive step

4.1. Independent claims

The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of **claims 12 and 17-20** does not involve an inventive step in the sense of Article 33(3)PCT.

a. The subject-matter of **claims 17-19** merely add routine modification options to the

subject-matter of claims 15 and 16 and is therefore obvious to a person skilled in the art. Taking in consideration the reasoning of point 3.2.1.a. only the vectors, cells and antibodies related to the sequences disclosed in claims 15 (a), (c) and (e) and 16 (a) are considered as to involve an inventive step, because there is no prior art which discloses or suggests these sequences.

b. A similar reasoning as above (paragraph 4.1.a.) applies to **claim 20**. To provide transformed cells which stably will express an polypeptide is a matter of routine and therefore obvious to a person skilled in the art. **100%** identity sequence with sequence **Seq-ID 6** and **99.7%** identity sequence with sequence **Seq-ID 4** are respectively disclosed in **D6** and **D4**.
Therefore, transformed cells with the vector expressing one of the following sequences : Seq-ID 6 ***per se*** and sequences having at maximum **99.7%** identity with sequence Seq-ID 4 and **85.3%** identity with Seq-ID 2 and derivative thereof are not inventive.

c. The subject-matter of **claim 12** merely add routine modification options to the subject-matter of **claims 1-4, 6 and 7** and is therefore obvious to a person skilled in the art. For this reason the subject-matter of **claims 12** does not involve an inventive step in the sense of Article 33(1) PCT.

4.2. Dependent claims

The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of **claims 5, 8, 10 and 13** does not involve an inventive step in the sense of Article 33(3)PCT.

a. The subject-matter of dependent **claims 5, 8 and 10** merely add routine modification options to the subject-matter of **claims 1-4, 6 and 7** and is therefore obvious to a person skilled in the art. For this reason the subject-matter of **claims 5, 8, 10** does not involve an inventive step in the sense of Article 33(1) PCT.

b. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of **claim 13** does not involve an inventive step in the sense of Article 33(3) PCT.

Document **D1** is the closest prior art (**D1**: all document).

The difference between the subject-matter of **claim 13** and that of **D1** is the fact that **D1** discloses GPR35 polypetides having only 72% identity to the Seq-ID 6 and 71% identity to the Seq-ID 2 (**D1**: claims 1 and 2, and sequences Seq-ID1 and 2).

The problem to be solved by **claim 13** may be regarded as how to identify compounds that modulate a GPR35 protein.
The solution to this problem can be seen as the provision of alternative GPR35 proteins.
There is no technical effect apparent from this difference.

Moreover, **D7** (D7: all the document) discloses a GPR35-Mouse sequence having **100%** identity with **Seq-ID 6.**
The skilled person being aware of D1 is prompted to look for closely related GPR35 proteins (like in D7), since D1 hints to the use of closely related GPR35 proteins (**D1**: page 3 paragraphs 26-33 and page 4).

Therefore, the subject-matter of **claim 13** does not involve an inventive step in the sense of Article 33(1) PCT.

However, none of the prior art document discloses or suggests at least 90% identity to the Seq-ID 2. Therefore, the subject-matter of the claim 13 (a)-(f) concerning the sequences with at least 90% identity to **Seq-ID 2** does involve an inventive step.

4. Clarity

a. The relative terms "substantially" used in e.g. **claims 4(b) and 7(b)** and the term "kind" of **claim 15** have no well-recognised meaning and leave the reader in doubt as to the meaning of the technical features to which they refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

b. The term "functional response" used in **claim 6** is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.